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STUDIES ON THE "SAN-HUANG-HSIEH-HSIN-TANG" IN THE TREATMENT OF ESSENTIAL HYPERTENSION

(Preliminary report)

HO-CHAN CHEN, MING-TSUEN HSIEH, HUEI-YANN TSAI,
HEN-HONG CHANG, TING-FU WANG*
and TAKESHI SHIBUYA**

The ancient Chinese formula of "San-Huang-Hsieh-Hsin-Tang" was for patients who have epigastric fullness, flushing, restlessness, constipation and a hard pulse. All these symptoms are frequently observed in patients with essential hypertension. We assessed the hypotensive effect of the formula. "San-Huang-Hsieh-Hsin-Tang" (specifically prepared from our laboratory), 500 mg tid, were given to 29 patients with mild to moderate essential hypertension for 2 weeks. This formula effectively lowered systolic/diastolic blood pressure to 140 mmHg±16 mmHg/88 mmHg±8 mmHg ($P<0.001$) from values of 167 mmHg±15 mmHg/108 mmHg±10 mmHg (Mean±S. D.). Heart rate also returned to the normal range. The subjective symptoms that improved were headache, flushed face, procordial distress and constipation. Two untoward effects were increased bowel movements and deep-yellow urine. However, they were reversible and not unpleasant.

Key words: ***Chinese herb, essential hypertension.***

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The formula of "San-Huang-Hsieh-Hsin-Tang" was originally described in Chin-Kuei-Yao-Lueh[1] for patients who have epigastric fullness, flushing, restlessness, constipation and a hard pulse. All these symptoms are frequntly observed in patients with essential hypertension. We assessed the hypotensive effect of the formula.

The components of the formula are Rheum *officinale*, Coptis *teeta* and Scutellaria *baicalensis*. We tested different combinations of the components to get the most benefit and least side effects. A modified "San-Huang-Hsieh-Hsin-Tang" was specifically prepared from our laboratory and then given to patients with essential hypertension for clinical trial to assess its benefits and drawbacks.

MATERIALS AND METHODS

Preparation of the "San-Huang-Hsieh-Hsin-Tang"

The mixture (1 kg) of powders of Rheum *officinale* BAILLON (*Polygonaceae*), Coptis *teeta* WALLICH (*Ranunculaceae*), Scutellaria *baicalensis* GEORGE (*Labiatae*), in the ratio of 1:2:3 were immersed in 5000 ml of 95% alcohol at room temperature for 3 days. The extract was evaporated and concentrated in a rotary vacuum evaporator at a temperature below 60°C. The sample was obtained by drying the concentrated extract at 80°-85° and then pulverizing through an No. 80* mesh.

* Hypertension Research Unit, China Medical College and Hospital, Taichung, Taiwan, Republic of China.
** Department of Pharmacology, Tokyo Medical College, Tokyo, Japan.
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Finally, the powder was packed into capsules.

Patients

Patients with essential hypertension meeting the following criteria were selected as our subjects:

(1) Blood pressure: Patients with persistent high blood pressure above 140 mmHg/90 mmHg during the observation period

(2) Severity of hypertension: Grades I and II by WHO standards[10]

(3) Age: 20 to 70 years

(4) Sex: Both male and female

Protocol

Fig. 1 shows the protocol of this study. In the first week, a placebo made of lactose was given. In the first 2 days of the first week, renal function (RFT), liver function (LFT), electrolyte balance and serum cholesterol/triglyceride were checked. Blood urea, serum creatinine and routine urinalysis were used as the indices of renal function. Serum SGOT-SGPT-LDH, albumin, globulin, bilirubin were used as the indices of liver function. Serum K^+, Na^+, Cl^- and Ca^{++} were used as the indices of electrolyte balance. Symptoms and signs were also recorded during this week. We measured the blood pressure of each patient to ascertain that this patient had elevated blood pressure. At the end of the first week, blood pressure and heart rate were recorded in a steady basal state. The specifically prepared "San-Huang-Hsieh-Hsin-Tang", 500 mg tid, was prescribed. Then the symptoms, signs, blood pressure and heart rate were monitored during a 2-week period. After 2 weeks, blood pressure, heart rate, renal function, liver function, electrolyte balance and serum cholesterol/triglyceride were re-checked again to see whether there were any changes in these parameters. Placebo was prescribed again to ascertain any return of high blood pressure and heart rate after withdrawing of "San-Huang-Hsieh-Hsin-Tang". After this week, "San-Huang-Hsieh-Hsin-Tang" was prescribed again to see the long-term effect of this formula.

PROTOCOL

Placebo	San-Huang-Tang	Placebo	San-Huang-Tang
1 week	2 weeks	1 week	continuing
(1) RFT and Electrolytes		(1) RFT and Electrolytes	
(2) LFT		(2) LFT	
(3) Chest P-A		(3) Chest P-A	
(4) BU routine		(4) BU routine	
(5) Cholesterol and Triglyceride		(5) Cholesterol and Triglyceride	
(6) Symptoms and Signs		(6) Symptoms and Signs	

Abbreviations: RFT: Renal function tests
LFT: Liver function tests
BU: Blood and urine
Chest P-A: Chest X-ray film, posterior-anterior view.

Fig. 1. The protocol for the clinical trial.

RESULTS

The effects of "San-Huang-Hsieh-Hsin-Tang" on blood pressure and heart rate

Table 1 shows the "San-Huang-Hsieh-Hsin-Tang" significantly lowered systolic/diastolic blood pressure to 140 mmHg ± 16 mmHg/88 mmHg ± 8 mmHg from values of 167 mmHg ± 15 mmHg/108 mmHg ± 10 mmHg (Mean ± S. D.), the "San-Huang-Hsieh-Hsin-Tang" significantly lowered heart rate to 73 beats ± 6 beats from values of 81 beats ± 7 beats (Mean ± S. D.) and after withdrawing "San-Huang-Hsieh-Hsin-Tang" for 1 week, blood pressure and heart rate returned back to 154 mmHg ± 15 mmHg/66 mmHg ± 7 mmHg, 76 beats ± 7 beats from values of 140 mmHg ± 16 mmHg/88 mmHg ± 8 mmHg, 73 beats ± 6 beats respectively. Blood pressure and heart rate did not return back to the original levels.

The effects of "San-Huang-Hsieh-Hsin-Tang" on serum cholesterol and triglyceride, electrolytes, side effects and improved symptoms

As shown in Table 2, there were mild decreases in the mean values of cholesterol/triglyceride, however, the differences were not statistically significant.

Before giving "San-Huang-Hsieh-Hsin-Tang", some patients exhibited hypokalemia which might be due to diuretics taken as one of the antihypertensive drugs in these patients. After 2 weeks of "San-Huang-Hsieh-Hsin-Tang", serum potassium levels became normal. This may indicate that "San-Huang-Hsieh-Hsin-Tang" does not influence the electrolyte balance in these patients.

Untoward effects after taking "San-Huang-Hsieh-Hsin-Tang" were few, reversible and not unpleasant. These untoward effects were increased bowel movements in 3 patients and deep-yellow urine in 11 patients.

The subjective symytoms improved were headache, heavy-headedness, neck-stiffness, flushed face, precordial distress and constipation.

The effects of "San-Huang-Hsieh-Hsin-Tang" on LFT and RFT

After patients took "San-Huang-Hsieh-Hsin-Tang" for 2 weeks, there were no apparent alterations in LFT and RFT.

DISCUSSION

Hypertension is one of the major causes of circulatory failure. Unfortunately, modern antihypertensive drugs all have their inevitable side-effects. Looking for a more desirable antihypertensive drug has been the goal of medico-pharmaceutical researchers.

The "San-Huang-Hsieh-Hsin-Tang" was reported, without statistical data, to have a hypotensive effect on animals.[2] In this study, we found it has a fairly good antihypertensive effect in patients with essential hypertension.

We tried the ratio of 1:1:1 of Rheum *officinale*, coptis *teeta* and Scutellaria *baicalensis*. This is the ratio originally described in Chin-Kuei-Yao-Lueh.[1] But we found that in some patients severe diarrhea resulted. We suspected that this was caused by the emodin in the Rheum *officinale*.[3] In large doses, Rheum *officinale* was reported to have only little hypotensive effect.[4] Berberine, Baicalin and Baicalein, the main constituents of Coptis *teeta* and Scutellaria *baicalensis* respectively,[5,6] were reported to have hypotensive effect.[7,5] Thereby, we decreased the amount of Rheum *officinale* and adopted the ratio of the 3 components: 1:2:3. By using this ratio, only 3 patients experienced increased bowel movements and this untoward effect was not unpleasant.

Aonuma[9] reported that "San-Huang-Hsieh-Hsin-Tang" could decrease the serum cholesterol/triglyceride in rabbits. In this study the mean values of cholesterol/triglyceride decreased but the differences were not statistically significant.

After withdrawing "San-Huang-Hsieh-Hsin-Tang" for 1 week blood pressure retuned half-way to the original level.

Table 1. Effects of "San-Huang-Hsieh-Hsieh-Hsin-Tang" on Blood Pressure and Heart Rate

Case	Age (y)	Sex	Blood Pressure (mmHg)			Heart Rate (beats/min)		
			Before[a]	After[b]	Withdraw[c]	Before[a]	After[b]	Withdraw[c]
1	38	F	150/100	136/82	139/86	85	80	85
2	42	F	152/110	138/90	140/98	80	72	78
3	45	F	178/102	130/88	154/100	87	82	84
4	60	M	150/90	140/86	146/90	80	70	78
5	53	M	190/124	136/94	166/100	70	74	73
6	60	F	198/122	178/98	186/102	73	70	70
7	54	M	162/96	138/88	142/90	80	80	79
8	56	M	148/108	142/96	158/104	81	80	78
9	59	F	154/90	138/74	170/94	71	70	70
10	51	M	160/108	134/92	138/98	84	70	76
11	56	M	182/114	160/90	170/100	100	80	84
12	53	M	178/102	160/100	170/102	85	70	78
13	27	M	168/92	140/88	142/94	82	77	90
14	58	F	182/98	178/84	178/92	90	72	84
15	40	F	168/98	160/90	164/96	73	74	72
16	34	M	190/130	120/90	164/110	88	72	80
17	37	M	168/104	134/84	158/100	92	72	74
18	58	M	160/100	144/88	152/88	72	66	66
19	59	M	188/114	152/90	166/100	76	60	61
20	52	M	156/106	124/76	144/88	86	84	84
21	65	F	186/105	132/84	166/98	80	78	78
22	50	M	164/106	118/88	132/96	78	60	66
23	60	M	171/121	157/107	158/108	83	79	78
24	63	M	170/111	120/72	132/86	92	69	74
25	70	M	150/108	130/84	144/90	80	76	80
26	53	M	144/110	134/90	146/94	74	69	72
27	62	F	160/115	124/76	130/80	79	76	80
28	57	M	170/120	146/88	152/98	77	64	70
29	46	M	156/114	126/84	156/102	76	72	72
Mean			167/108	140/88	154/96	81	73	76
Standard Deviation			15/10	16/8	15/7	7	6	7
T value			6.6/8.3		6/8.5	4.7		2.9
P value			<0.001		<0.001	<0.001		<0.01

* Abbreviations: F: Female
M: Male
a: Measured 1 week before drug treatment
b: After 2-week drug treatment
c: 1 week after withdrawal of the drug

Table 2. Effects of "San-Huang-Hsieh-Hsin-Tang" on Serum Cholesterol and Triglyceride, Electrolytes, Side Effects and Improved Symptoms

Case	Cholesterol/ Triglyceride		Electrolytes		Side Effects	Improved Symptoms
	Before	After	Before	After		
1	200/102	180/100	N	N	Increased bowel movement	Headache, Heavy headedness, Flushed face
2	163/206	160/174	$K^+\downarrow$	N	None	Precordial distress, Flushed face
3	210/170	210/168	N	N	None	Constipation
4	206/307	204/111	N	N	None	Constipation
5	178/304	179/293	N	N	Increased bowel movement	Flushed face, Heavy headedness, precordial distress
6	182/278	180/206	N	N	Deep yellow urine	Constipation
7	229/226	230/219	N	N	Deep yellow urine	Precordial distress
8	254/219	256/205	$K^+\downarrow$	N	None	Headache
9	221/223	234/240	N	N	None	Constipation
10	174/134	184/150	N	N	None	Neck stiffness
11	358/141	202/108	N	N	None	Heavy headedness
12	188/95	191/100	$K^+\downarrow$	N	Deep yellow urine	Constipation
13	170/110	146/95	N	N	None	Constipation, precordial distress
14	242/488	250/400	$K^+\downarrow$	N	None	Constipation
15	168/107	180/104	N	N	None	Precordial distress
16	245/206	166/150	$K^+\downarrow$	N	Increased bowel movement	Neck stiffness, Fatigue, Impotency
17	215/325	201/242	N	N	None	Neck stiffness, Palpitation
18	241/109	252/156	$K^+\downarrow$	N	Deep yellow urine	Neck stiffness
19	202/117	263/97	N	N	Deep yellow urine	Neck stiffness
20	205/234	181/54	N	N	None	Heavy headedness, Fatigue
21	269/196	199/194	N	N	None	Numbness of fingers, Nocturia
22	206/207	191/184	$K^+\downarrow$	N	Deep yellow urine	Neck stiffness
23	269/190	223/147	N	N	Deep yellow urine	None
24	196/110	197/100	$K^+\downarrow$	N	Deep yellow urine	Precordial distress
25	221/263	209/145	$K^+\downarrow$	N	None	Heavy headedness, precordial distress, Impotency
26	186/100	181/77	$K^+\downarrow$	N	None	Neck stiffness, Epigastric fullness
27	216/120	247/140	N	N	Deep yellow urine	Palpitation
28	237/193	239/145	N	N	Deep yellow urine	Impotency, Fatigne, Neck stiffness, Hemorrhoids
29	234/283	187/195	N	N	Deep yellow urine	Constipation, Neck stiffness, Flushed face, Impotency
Mean	217/198	204/162	* Abbreviations: LFT: Liver Function Tests			
Standard Deviation	40/90	31/72	RFT: Renal Function Tests			
T value	1.4/1.7		N: Within Normal limits			
P value	>0.1/>0.05		$K^+\downarrow$: Decreased Serum Potassium Level			

This indicates that "San-Huang-Hsieh-Hsin-Tang" lowers blood pressure but does not cure essential hypertension, just like all other antihypertensive drugs. However, it is important to lower blood pressure in hypertensive patients because epidemiological studies show that lowering blood pressure in hypertensive patients decreases mortality and morbidity in these patients owing to decreased loading on the cardiovascular system.

Our further work is to use "San-Huang-Hsieh-Hsin-Tang" widely in patients with essential hypertension, to assess its therapeutic effects and to study its mechanism and toxicology.

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三黃瀉心湯治療本態性高血壓之研究

陳和昌　謝明村　蔡輝彥　張恒鴻
王廷輔*　澁谷　健**

中國古方「三黃瀉心湯」的適應症包括：腹壁阻抗强，表面柔軟，心下痞硬，顏面紅潮，煩躁不安，便秘，脈搏有力等。這些症狀也常見於本態性高血壓患者，我們擬對該處方的降壓效果加以評估。

篩選29位中等度本態性高血壓患者，男性20例，女性9例，年齡分佈自27歲到70歲，平均爲52歲；以本院製備之三黃瀉心湯(大黃、黃連、黃芩) 500毫克，一日3次，連續給藥2週，發現心搏率及血壓都有明顯的下降：血壓由對照值 167±15/108±10 mm Hg 降到 140±16/88±8 mm Hg (平均值±標準偏差)。血壓測定是在病人來門診後，先休息20分鐘，然後測量3次取平均值爲準。主觀症狀改善者有：頭痛、顏面潮紅，心區不適、便秘。副作用包括腸蠕動增加及小便顏色變黃，但停藥卽可恢復，亦未引起不適。

* 中國醫藥學院，高血壓研究小組，中國藥學研究所
** 日本、東京，東京醫科大學，藥理學教室
民國73年2月7日受理